AFRL-HE-BR-TR-2007-0064

SERUM DIOXIN AND MEMORY AMONG VETERANS OF OPERATION RANCH HAND

Johnson Patches
Martin Cary
William Grubbs
William Jackson
Julie Robinson
Marian Pavuk

Air Force Research Laboratory
Human Effectiveness Directorate

September 2007

Air Force Research Laboratory
Human Effectiveness Directorate
Directed Energy Bioeffects Division
Brooks City-Base, TX 78235.

NOTICE AND SIGNATURE PAGE

This report is published in the interest of scientific and technical information exchange and does not constitute approval or disapproval of its ideas or findings.

This report is published as received and has not been edited by the publication staff of the Air Force Research Laboratory.

Using Government drawings, specifications, or other data included in this document for any purpose other than Government-related procurement does not in any way obligate the US Government. The fact that the Government formulated or supplied the drawings, specifications, or other data, does not license the holder or any other person or corporation, or convey any rights or permission to manufacture, use, or sell any patented invention that may relate to them.

This report was cleared for public release by the Air Force Research Laboratory, Brooks City-Base, Public Affairs Office and is available to the general public, including foreign nationals. Copies may be obtained from the Defense Technical Information Center (DTIC) (http://www.dtic.mil).

AFRL-HE-BR-TR-2007-0064 HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION IN ACCORDANCE WITH ASSIGNED DISTRIBUTION STATEMENT.

_____//SIGNED//_____
JULIE ROBINSON, GS-14, DAF
Principal Investigator, Air Force Health Study

_____//SIGNED//_____
GARRETT D. POLHAMUS, DR-IV, DAF
Chief, Directed Energy Bioeffects Division

This report is published in the interest of scientific and technical information exchange, and its publication does not constitute the Government's approval or disapproval of its ideas or findings.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From – To)*
18-09-2006	Technical Report	January 1982 – November 2006

4. TITLE AND SUBTITLE

Serum Dioxin and Memory Among Veterans of Operation Ranch Hand

5a. CONTRACT NUMBER
F41624-01-C-1012

5b. GRANT NUMBER
N/A

5c. PROGRAM ELEMENT NUMBER
0605356F

6. AUTHOR(S)
Patches Johnson, Martin Cary, William Grubbs, William Jackson, Julie Robinson, Marian Pavuk

5d. PROJECT NUMBER
2767

5e. TASK NUMBER
00

5f. WORK UNIT NUMBER
F1

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
AFRL/HED
2655 Flight Nurse Road
Brooks City-Base, TX 78235-5137

8. PERFORMING ORGANIZATION REPORT NUMBER
N/A

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
SAIC
5203 Leesburg Pike, Suite 1500
Falls Church, VA 22041

10. SPONSOR/MONITOR'S ACRONYM(S)
AFRL/HED

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
AFRL-HE-BR-TR-2007-0064

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release. Public Affairs Case File No. 06-404, Nov 8, 2006

13. SUPPLEMENTARY NOTES
None

14. ABSTRACT We used the Wechsler Memory Scale & the Wechsler Memory Scale-Revised to assess memory among Air Force (AF) veterans exposed to Agent Orange & its contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), during the Vietnam War. The index subjects were veterans of Operation Ranch Hand (RH), the unit responsible for aerial herbicide spraying in Vietnam from 1962 to 1971. A comparison group of other AF veterans, who served in Southeast Asia during the same period, but were not involved with spraying herbicides, served as referents. Memory was assessed during AF Health Study examinations in 1982 and 2002 and dioxin levels were measured in 1987, 1992, 1997, or 2002. We assigned each RH veteran to the background, low, or high dioxin exposure category on the basis of a measurement of dioxin body burden. Although we found that the immediate recall portion of the Logical Memory subtest of the Wechsler Memory Scale was decreased among veterans with the highest dioxin exposure in 1982, the results of this study indicate that Agent Orange-exposed RH veterans were functioning normally in regards to immediate and delayed memory in 2002. No relation between the dioxin exposure and the change in memory function between 1982 and 2002 was observed. There does not appear to be any long-term adverse effect in regards to memory functioning. The specific neurological mechanisms (e.g., structural, neurochemical, or other) related to the cause of the 1982 deficits in memory are unknown; however, these changes likely have been reversed.

15. SUBJECT TERMS
Dioxin; epidemiology; herbicide; memory; TCDD; Weschsler Memory Scale

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			Julie Robinson
Unclassified	Unclassified	Unclassified	SAR	20	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

This page left intentionally blank

Serum Dioxin and Memory Among Veterans of Operation Ranch Hand

Patches Johnson[1], Martin Cary[2], William Grubbs[2], William Jackson[3], Julie Robinson[3], Marian Pavuk[4]

[1]Roanoke College, Salem, VA, USA
[2]SAIC, Falls Church, VA, USA
[3]Air Force Research Laboratory, Brooks City-Base, TX, USA
[4]SpecPro Inc., San Antonio, TX, USA

Abstract

We used the Wechsler Memory Scale and the Wechsler Memory Scale-Revised to assess memory among Air Force veterans exposed to Agent Orange and its contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), during the Vietnam War. The index subjects were veterans of Operation Ranch Hand, the unit responsible for aerial herbicide spraying in Vietnam from 1962 to 1971. A comparison group of other Air Force veterans, who served in Southeast Asia during the same period, but were not involved with spraying herbicides, served as referents. Memory was assessed during Air Force Health Study examinations in 1982 and 2002 and dioxin levels were measured in 1987, 1992, 1997, or 2002. We assigned each Ranch Hand veteran to the background, low, or high dioxin exposure category on the basis of a measurement of dioxin body burden. Although we found that the immediate recall portion of the Logical Memory subtest of the Wechsler Memory Scale was decreased among veterans with the highest dioxin exposure in 1982, the results of this study indicate that Agent Orange-exposed Ranch Hand veterans were functioning normally in regards to immediate and delayed memory in 2002. No relation between the dioxin exposure and the change in memory function between 1982 and 2002 was observed. There does not appear to be any long-term adverse effect in regards to memory functioning. The specific neurological mechanisms (e.g., structural, neurochemical, or other) related to the cause of the 1982 deficits in memory are unknown; however, these changes likely have been reversed.

Author Keywords: Dioxin; Epidemiology; Herbicide; Memory; TCDD, Wechsler Memory Scale

INTRODUCTION

To address the concerns of veterans, Congress, and the public about the consequences of exposure to Agent Orange and its contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), the Air Force has been conducting a 20-year prospective study of veterans of Operation Ranch Hand, the unit responsible for handling and aerial spraying of herbicides in Vietnam from 1962 to 1971. These veterans were exposed to herbicides while filling spray tanks, maintaining the aircraft and spray equipment, and in flight. Agent Orange, comprising approximately 60 percent of the 19 million gallons of herbicides sprayed in Vietnam, was a 1:1 mixture of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid and was contaminated from less than 0.05 to almost 50 parts per million (ppm) with 2,3,7,8-tetrachlorodibenzo-p-dioxin (Institute of Medicine, 1994).

Shortly after the end of the Vietnam War, the Air Force began studying the effects of herbicides, specifically Agent Orange, on those servicemen who were members of Operation Ranch Hand. These veterans were assigned the task of defoliating designated areas of Vietnam and, thus, became exposed to dioxin to varying degrees. The Air Force Health Study (AFHS) performed examinations in 1982, 1985, 1987, 1992, 1997, and 2002, which rigorously studied numerous medical and psychological variables looking for associations between health outcomes and herbicide and dioxin exposure. Participation was voluntary and written informed consent was obtained at the examination site after the participants were given a complete description of the study and a full explanation of all procedures. Barrett et al. (2001) found decreased memory functioning, particularly in those Ranch Hand participants with the highest dioxin exposure.[111] Other studies have indicated memory problems associated with dioxin exposure (Peper, 1993; Pelclova, 2001). In this article, we further examined the memory functioning of the AFHS veterans exposed to dioxin, based on both analysis of 2002 AFHS examination results and the relation of results at the 1982 and 2002 AFHS examinations.

MATERIALS AND METHODS

Study design and subject selection procedures for the AFHS are published elsewhere (Wolfe et al., 1990). The goal of the AFHS is to determine whether veterans of Operation Ranch Hand have experienced adverse health effects due to exposure to herbicides (not all herbicides sprayed were contaminated with dioxin or their dioxin contaminant). Health indices and the cumulative mortality experience of Ranch Hand veterans have been contrasted with those of a comparison group of Air Force veterans who served in Southeast Asia (SEA) during the same period as Ranch Hand veterans, but were not involved with spraying herbicides. Comparison veterans were matched to Ranch Hand veterans based on age, race, and military occupation. All Ranch Hand and comparison veterans are male.

Dioxin Assessment

During the 1987 examination, consent was obtained from veterans and their blood was collected and assayed to determine dioxin levels (Grubbs et al., 1996), which was to be used as a surrogate measure of exposure to herbicides. Veterans with no quantifiable dioxin result in 1987, those who refused dioxin testing in 1987, and those new to the study in 1992 also were asked to give blood for the assay at the 1992 examination. A similar request was made for veterans at the 1997 and 2002 examinations for whom blood was not available for dioxin testing.

Some veterans were removed from all analyses. Table 1 shows study-size reductions by group for the 1982 and 2002 examinations. Three veterans were examined but determined after the 2002 examination to be ineligible for participation in the AFHS. A lipid measurement was not available for one Ranch Hand. One veteran's cognitive test results were considered invalid because he had been diagnosed with epilepsy prior to the 1982 physical examination. Memory data were unavailable for 127 veterans at the 1982 examination and 3 veterans at the 2002 examination. One Ranch Hand veteran did not have a lipid measurement on the serum collected for dioxin testing; thus, a dioxin measurement was not able to be determined for him. Dioxin results were collected in the 1987 and subsequent examinations, but 83 veterans who participated in the 1982 examination did not have lipid-adjusted dioxin measured in the later examinations.

Table 1.
Sample size reduction by group among AFHS veterans

	1982 Examination			2002 Examination		
	Ranch Hand	Comparison	Total	Ranch Hand	Comparison	Total
Examined	1046	1223	2269	778	1176	1954
Ineligible	(1)	(1)	(2)	(1)	(2)	(3)
Invalid cognitive results	(1)	(0)	(1)	(1)	(0)	(1)
No available memory data	(12)	(115)	(127)	(1)	(2)	(3)
Lipid measurement not available	(1)	(0)	(1)	(1)	(0)	(1)
Unable to classify dioxin (Ranch Hands)	(83)	(0)	(83)	(0)	(0)	(0)
Included in analysis	948	1107	2055	774	1172	1946

We conducted a primary and an alternative analysis. In the primary analysis, we estimated the initial dioxin dose at the end of the last tour of duty in Vietnam in Ranch Hand veterans having first-measured dioxin levels greater than 10 parts per trillion (ppt) using a first-order model with a constant half-life of 7.6 years

(Michalek and Tripathi, 1999). We assigned each veteran to one of four exposure categories: "comparison," "background," "low," and "high." The "comparison" category comprised comparison veterans, regardless of whether the veteran had a measured dioxin level or what that level was. The "background" category comprised Ranch Hand veterans with a 1987, 1992, 1997, or 2002 dioxin measurement of less than or equal to 10 ppt. Ranch Hand veterans with a 1987, 1992, 1997, or 2002 dioxin measurement greater than 10 ppt were assigned to "low" or "high" dioxin categories if their initial dioxin levels were less than or equal to 117.6 ppt or greater than 117.6 ppt, respectively. The cut point separating the "low" and "high" categories (117.6 ppt) was the median initial dioxin level among all Ranch Hand veterans who attended the 2002 examination and had 1987, 1992, 1997, or 2002 dioxin levels greater than 10 ppt. Table 2 shows the four subgroups and the number of veterans and percentage of the total number of veterans included in the analysis in each subgroup for veterans at the 1982 examination (*n*=2,055), veterans at the 2002 examination (*n*=1,946), and veterans who attended either the 1982 or 2002 examinations (*n*=2,436).

Table 2.
Distribution of AFHS veterans by examination and dioxin exposure category

Subgroup	1982 Examination Veterans (n=2,055)	2002 Examination Veterans (n=1,946)	1982 or 2002 Examination Veterans (n=2,436)
Comparison	1,107 (53.9%)	1,172 (60.2%)	1,427 (58.6%)
Background (Ranch Hand)	403 (19.6%)	351 (18.0%)	442 (18.1%)
Low (Ranch Hand)	271 (13.2%)	210 (10.8%)	282 (11.6%)
High (Ranch Hand)	274 (13.3%)	213 (10.9%)	285 (11.7%)

In the alternative analysis, we included all veterans who attended either the 1982 or the 2002 examination who had a dioxin level measured at some time during the AFHS (Ranch Hand: *n*=1,009, comparison: *n*=1,427) and stratified the combined cohort by quintiles of the distribution of the measured dioxin level. This approach accounted for dioxin exposure from any source regardless of whether the veteran was a Ranch Hand or comparison. Veterans with nonquantifiable dioxin levels were assigned a level equal to the limit of quantitation divided by the square root of 2 (Hornung and Reed, 1990). Veterans with dioxin levels below the limit of detection were calculated as the limit of detection divided by the square root of 2 (Hornung and Reed, 1990). The dioxin quintiles, in ppt, were (1) 0≤dioxin≤2.90; (2) 2.90<dioxin≤4.29; (3) 4.29<dioxin≤6.23; (4) 6.23<dioxin≤13.11; and (5) 13.11<dioxin≤617.75.

These quintiles represent dioxin levels that divide the Ranch Hand and comparison veterans who attended either the 1982 or the 2002 examination into five subgroups, with each subgroup comprising approximately 20 percent of the veterans. The number of veterans in each of these groups is different when the 1982 and 2002 examinations are analyzed separately. Table 3 shows the five subgroups and the number of veterans and percentage of the total number of veterans in each subgroup for veterans included in the analysis at the 1982 examination (*n*=2,055), veterans at the 2002 examination (*n*=1,946), and veterans who attended either the 1982 or 2002 examinations (*n*=2,436). As compared to veterans at the 1982 examination, a greater percentage of veterans at the 2002 examination were in the subgroups with the lower dioxin levels. The distributional shift to veterans with lower dioxin levels is probably due to the decrease in Ranch Hand participation over time and the strategy of replacing comparisons to maintain the size of the AFHS population.

Table 3.
Distribution of AFHS veterans by examination and dioxin quintile

Subgroup	1982 Examination Veterans (n=2,055)	2002 Examination Veterans (n=1,946)	1982 or 2002 Examination Veterans (n=2,436)
0 ppt≤dioxin≤2.90 ppt	320 (15.6%)	419 (21.5%)	486 (20.0%)
2.90 ppt<dioxin≤4.29 ppt	396 (19.3%)	400 (20.6%)	486 (20.0%)
4.29 ppt<dioxin≤6.23 ppt	417 (20.3%)	380 (19.5%)	490 (20.1%)
6.23 ppt<dioxin≤13.11 ppt	453 (22.0%)	384 (19.7%)	485 (19.9%)
13.11 ppt<dioxin≤617.75 ppt	469 (22.8%)	363 (18.7%)	489 (20.1%)

Memory Assessment

To assess memory function, the Wechsler Memory Scale (WMS) (Wechsler, 1945) was administered at the 1982 examination and the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987) at the 2002 examination. The WMS and the WMS-R are individually administered clinical instruments for appraising major dimensions of memory functions in adolescents and adults. The functions assessed include memory for verbal and figural stimuli, meaningful and abstract material, and delayed as well as immediate recall. The WMS was developed to permit clinicians in different settings and at different times to assess the same memory functions of their patients.

The original instrument provided a base from which further editions of the Wechsler Memory Scale would develop. This original test, however, had several limitations (Russell, 1975; Prigatano, 1977 and 1978), such as an emphasis on verbal memory versus visual recall. In addition, scoring criteria were not sufficiently detailed on the logical memory and visual reproductions subtests.

In 1987, the WMS-R was published, expanding on the original WMS and creating a more thorough and reliable instrument for assessing memory. Wechsler completed the major changes before his death in 1981. The WMS-R added new subtests and refined old subtests, revised scoring criteria, and identified age-related norms. Three subtests were administered for both the AFHS 1982 and 2002 examinations: the Verbal Paired Associates subtest, the Logical Memory subtest (immediate and delayed recall), and the Visual Reproduction subtest (immediate and delayed recall).

In the Verbal Paired Associates subtest (called Associate Learning on the WMS), which was designed to assess verbal retention, the veteran learned word pairs, some of which reflected easy associations (e.g., metal – iron), while others were more difficult (e.g., crush – dark). The WMS-R Verbal Paired Associates subtest was different from the WMS subtest in that only eight word pairs (four easy and four hard) were used. On the WMS, 10 word pairs, 6 easy and 4 hard, were used. Both versions presented paired associations three times. Scoring criteria gave one point for each correct answer on the WMS-R, regardless of the difficulty of the pair, while only half a point was given for correct easy pairs and one point was given for correct hard pairs on the WMS.

The Logical Memory subtest for the WMS and the WMS-R assesses recall of logical verbal material and includes two brief stories that were read to the veterans individually. After each story, the veteran retold the story from memory (immediate recall). Following a delay of 30 minutes, the veteran was again asked to relate each story (delayed recall). The overall score for the Logical Memory subtest for the WMS was the average of the scores on the two stories, whereas the overall score on the WMS-R was the sum of the scores on the two stories. The scoring was the same for the immediate and delayed recall. The WMS-R Logical Memory subtest is different from the WMS Logical Memory subtest in that the first story was modified to eliminate dated references and the second story was entirely new and designed to be of equal difficulty as the first story. The scoring criteria for each story also were much more detailed for the WMS-R.

For the Visual Reproduction subtest, designed to assess visual memory, the veteran was asked to draw from memory four simple geometric designs that were each exposed for 10 seconds (immediate recall). Following a delay of 30 minutes, the veteran was again asked to draw each design (delayed recall). The overall score on the Visual Reproduction subtest of the WMS and the WMS-R was the sum of the scores on the four designs. The scoring was the same for the immediate and delayed recall. The Visual Reproduction subtest on the WMS-R is different from the WMS Visual Reproduction subtest in that the final drawing from the WMS was eliminated and two new drawings were added. The scoring system for the designs was more detailed with numerous examples used to improve the accuracy of the scores. The AFHS used only four of the five designs from the WMS-R at the 2002 examination to preserve consistency with the WMS from the 1982 examination.

The Wechsler Memory Scale–Third Edition (Wechsler, 1997) was developed in 1997 and made even more extensive revisions to the WMS. The WMS-R subtests were chosen for the AFHS 2002 examination, however, because the changes in the subtests from the WMS, especially the improved scoring criteria, provided important improvements, while still retaining close similarity to the WMS subtests that had been used for the 1982 examination.

Data Analysis

In the primary analysis, we contrasted mean scores on the memory scales in the Ranch Hand background, low, and high dioxin exposure categories with those in the comparison category, adjusting for the following: body mass index at time of the dioxin blood draw; military occupation (officer, enlisted flyer, enlisted groundcrew); age (in years at the time of the 1982 and 2002 physical examinations); race (black, non-black); drinking history (drink-years); marital status (married, unmarried); education (high school, college); combat exposure quartile; organic psychotic conditions, including dementia, alcoholic withdrawal delirium, drug withdrawal syndrome, and acute delirium (yes, no); other psychoses (yes, no); neurotic personality and other nonpsychotic disorders (yes, no); substance abuse (yes, no); and use of psychotropic medications. We assessed the significance of contrasts on continuously distributed outcomes using differences of least-square means and the mean-squared error arising from linear models. In an alternative analysis, we contrasted the second, third, fourth, and fifth dioxin quintiles with the first quintile with regard to the same memory scales using the aforementioned adjustment variables.

We defined a drink-year as drinking one 2-ounce shot of 80-proof whiskey, 12 ounces of beer, or 5 ounces of wine per day for 1 year. Race (black, non-black) was determined from military records, as was military occupation (officer, enlisted flyer, enlisted groundcrew). Military occupation was associated with both education and training. Education was dichotomized as high school-educated or college-educated. Veterans with an Associate of Arts degree or higher were classified as college-educated. Most officers were college-educated; most enlisted personnel were high school-educated. Enlisted flyers were trained for flight status, while enlisted groundcrew were not.

We assessed combat exposure with a combat index designed for the AFHS. The combat index was computed as a weighted sum of indicators of positive responses to 15 questions, with positive (yes) responses indicated by 1 or 2 and negative (no) responses indicated by 0. The questions (and weights) were as follows: Did you receive combat pay? (1), Crash land or bail out or were you shot down? (1), Receive sniper or sapper fire in or around the base? (1), Move killed or wounded personnel? (2), Serve as a forward air controller? (1), Fly the same aircraft when a fellow crew member was wounded or killed? (2), Fly in the same formation or the same sortie when a fellow crew member was wounded or killed? (1), Fly an aircraft that received battle damage? (1), Receive incoming artillery or rocket fire at your home base or camp? (1), Encounter mines or

booby traps? (1), Engage Viet Cong (VC) or North Vietnamese Army (NVA) in a firefight? (2), Did you kill VC or NVA in strafing or bombing runs? (2), Were you wounded? (2), Captured by the enemy? (2), Was a close friend killed in action? (2). Each veteran was assigned to one of four strata depending on whether his sum fell into the ranges 0–2, 3–5, 6–8, or 9 or greater, the approximate quartiles of the distribution.

We collected information on psychiatric diagnoses and psychotropic medication use during the 1982 physical examination. If the veteran reported that he had experienced mental or emotional illnesses, his written consent was obtained to access medical records to verify the diagnosis. We classified psychiatric diagnoses according to International Classification of Disease (ICD) codes following the ICD-9-Clinical Modification convention (Puckett, 1995). Four dichotomous (yes, no) variables for each of the following categories of psychiatric diagnoses were determined by medical record review: (1) organic psychotic conditions, including dementia, alcoholic withdrawal delirium, drug withdrawal syndrome, and acute delirium (ICD codes 290–294), (2) other psychoses (ICD codes 295–299), (3) neurotic personality and other nonpsychotic disorders (ICD codes 306–316, 300–302), and (4) substance abuse (ICD codes 303–305). We defined an indicator for the use of psychotropic medications (yes, no) using American Hospital Formulary Service codes (Board of the American Society of Health-System Pharmacists, 2000) and by reviewing medical records; a veteran was assigned the value "yes" for this variable if he was taking psychotherapeutic agents (formulary code 28:16), anti-manic agents (formulary code 28:28), or anxiolytics, sedatives, or hypnotics (formulary code 28:24) at any time during the postservice period beginning with departure from SEA.

The actual scores from the memory scales were used in the individual analyses of the 1982 and 2002 examinations. A different strategy was necessary, however, when the scales from the 1982 and 2002 examinations were contrasted with each other because of the inherent difference in the scoring methods, as explained in the Memory Assessment section. The mean and standard deviation for each memory scale was determined at each examination. The scores from the memory scales were then standardized by subtracting the mean from each score and dividing by the associated standard deviation. Analysis results for the memory scales shown in the next section, therefore, are based on the actual scores for the 1982 and 2002 examinations and standardized scores for the comparison of the 1982 and 2002 examinations.

All analyses were conducted using SAS® software (SAS/STAT®, 1999). Repeated measures analyses (Littell et al., 1996) and general linear models analyses (SAS/STAT®, 1999) were used to compare data between the 1982 and 2002 examinations. We used main effects models with no stepwise reduction throughout (Kleinbaum et al., 1982).

RESULTS

Dioxin and Demographic Characteristics

The distributions of military occupation and demographics are presented in Table 4. Ranch Hand veterans in the high dioxin category were younger on average than those in the low, background, or comparison categories. Most of the veterans with high dioxin levels were enlisted groundcrew; most with background levels were officers.

Table 4.
Distribution of dioxin and demographic characteristics for AFHS veterans at the 1982 and 2002 examinations by dioxin exposure category

Characteristic	Comparison	Ranch Hand		
		Background	Low	High
Sample size[a]				
1982	1,107	403	271	274
2002	1,172	351	210	213
Dioxin (median [range])[b]				
1982	4.1 (0.4-54.8)	5.7 (0.4-10.0)	65.3 (32.2-117.4)	242.9 (117.9-4221.9)
2002	3.7 (0.4-32.3)	5.7 (0.4-10.0)	64.8 (33.0-116.9)	250.7 (118.5-4221.9)
Age (in years) (mean [SD])				
1982	43.9 (7.7)	44.6 (7.4)	45.2 (7.6)	40.9 (7.2)
2002	63.0 (7.0)	64.1 (7.0)	64.5 (7.0)	60.1 (6.8)
Race (Black [%])				
1982	6.1	5.0	7.7	4.7
2002	6.5	5.1	9.5	4.7
Military occupation				
Officer (%)				
1982	37.8	59.8	39.5	2.9
2002	39.4	61.8	40.0	2.8
Enlisted flyer (%)				
1982	16.0	12.2	21.4	21.5
2002	15.7	12.3	22.4	19.7
Enlisted groundcrew (%)				
1982	46.2	28.0	39.1	75.6
2002	44.9	25.9	37.6	77.5

[a]Sample size for 1982 is based on 2,055 veterans who had a dioxin measurement and either a Verbal Paired Associates, Logical Memory (immediate or delayed recall), or Visual Reproduction (immediate or delayed recall) subtest score from the 1982 examination; sample size for 2002 is based on 1,946 veterans who had a dioxin measurement and either a Verbal Paired Associates, Logical Memory (immediate or delayed recall), or Visual Reproduction (immediate or delayed recall) subtest score from the 2002 examination.

[b]Measured (in ppt) in 1987, 1992, 1997, or 2002 in comparison and Ranch Hand background categories, extrapolated to end of service in Vietnam in Ranch Hand low and high categories.

SD = standard deviation.

Memory

Some indication that memory function may have been affected among the veterans in the high dioxin category (Table 5) existed at the 1982 examination. Ranch Hand veterans in the high category scored significantly lower than comparison veterans on the immediate recall trial of the WMS Logical Memory subtest, a result that was reported previously (Barrett et al., 2001). The previous paper also reported that

Ranch Hand veterans in the high category scored significantly lower than comparison veterans on the delayed recall trial of the WMS Logical Memory subtest. The analysis for this article additionally included education as a covariate. Data from 94 veterans who did not have a dioxin measurement when the 2001 article was written, but who now have a dioxin measurement, also were included. These modifications to the analysis resulted in the significance level changing from p=0.04 for the 2001 article to p=0.08 for this article. Of these 94 veterans, 69 were Comparisons and 25 were Ranch Hands. Three of these 25 Ranch Hands were in the high dioxin exposure category. The Comparison mean decreased with the inclusion of these veterans, while the mean of Ranch Hands in the high dioxin exposure category was almost identical. Consequently, the difference between Ranch Hands in the high dioxin exposure category and Comparisons narrowed with the inclusion of these 94 veterans and the difference became nonsignificant.

There were no indications, however, that memory function was affected by dioxin at the 2002 examination (Table 6). Although nonsignificant, Ranch Hand veterans usually scored higher, on average, than comparisons on all memory scales at this examination.

Table 5.
Adjusted[a] Wechsler Memory Scale results by dioxin category for the 1982 examination

Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
Verbal Paired Associates				
Sample Size	1,095	397	264	266
Adjusted Mean[a]	16.07	16.03	15.87	15.98
Difference of Adjusted Means	0	-0.04	-0.19	-0.09
95% Confidence Interval		-0.39,0.31	-0.59,0.21	-0.50,0.33
P-value		0.83	0.35	0.68
Logical Memory				
Immediate Recall				
Sample Size	1,044	379	254	252
Adjusted Mean[a]	6.56	6.41	6.38	6.12
Difference of Adjusted Means	0	-0.15	-0.18	**-0.44**
95% Confidence Interval		-0.49,0.20	-0.57,0.21	**-0.85,-0.04**
P-value		0.40	0.37	**0.03**
Logical Memory				
Delayed Recall				
Sample Size	1,067	386	266	259
Adjusted Mean[a]	4.51	4.55	4.24	4.16
Difference of Adjusted Means	0	0.05	-0.27	-0.34
95% Confidence Interval		-0.28,0.37	-0.63,0.10	-0.73,-0.04
P-value		0.77	0.15	0.08
Visual Reproduction				
Immediate Recall				
Sample Size	1,096	396	267	265
Adjusted Mean[a]	7.98	8.15	8.08	7.98
Difference of Adjusted Means	0	0.17	0.10	0
95% Confidence Interval		-0.12,0.45	-0.23,0.42	-0.34,0.33
P-value		0.25	0.55	0.98
Visual Reproduction				
Delayed Recall				
Sample Size	1,100	398	268	266
Adjusted Mean[a]	6.75	6.93	6.79	6.71

Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
Difference of Adjusted Means	0	0.18	0.04	-0.04
95% Confidence Interval		-0.16,0.52	-0.34,0.43	-0.44,0.36
P-value		0.29	0.82	0.84

[a]Adjusted for body mass index at time of the dioxin blood draw, military occupation, age, race, combat exposure, drink-years, marital status, education, organic psychotic conditions, other psychoses, neurotic personality and other nonpsychotic disorders, substance abuse, and use of psychotropic medications.

Note: Values in bold indicate a statistically significant result.

Table 6. Adjusted[a] Wechsler Memory Scale-Revised results by dioxin category for the 2002 examination

Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
Verbal Paired Associates				
Sample Size	1,165	350	209	211
Adjusted Mean[a]	15.56	15.63	15.49	15.60
Difference of Adjusted Means	0	0.07	-0.07	0.05
95% Confidence Interval		-0.38,0.51	-0.60,0.46	-0.50,0.59
P-value		0.76	0.79	0.87
Logical Memory Immediate Recall				
Sample Size	1,165	350	209	211
Adjusted Mean[a]	20.74	20.75	21.44	20.76
Difference of Adjusted Means	0	0.02	0.71	0.02
95% Confidence Interval		-0.76,0.80	-0.23,1.64	-0.94,0.98
P-value		0.96	0.14	0.97
Logical Memory Delayed Recall				
Sample Size	1,164	350	209	211
Adjusted Mean[a]	15.32	15.48	16.06	15.79
Difference of Adjusted Means	0	0.16	0.74	0.47
95% Confidence Interval		-0.69,1.02	-0.29,1.76	-0.58,1.53
P-value		0.71	0.16	0.38
Visual Reproduction Immediate Recall				
Sample Size	1,163	350	209	211
Adjusted Mean[a]	25.36	25.41	25.62	25.53
Difference of Adjusted Means	0	0.06	0.26	0.17
95% Confidence Interval		-0.49,0.61	-0.40,0.92	-0.50,0.85
P-value		0.84	0.44	0.62
Visual Reproduction Delayed Recall				
Sample Size	1,163	350	209	211
Adjusted Mean[a]	22.02	22.27	22.60	22.30
Difference of Adjusted Means	0	0.25	0.58	0.27
95% Confidence Interval		-0.47,0.97	-0.29,1.44	-0.61,1.16

Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
P-value		0.50	0.19	0.54

[a]Adjusted for body mass index at time of the dioxin blood draw, military occupation, age, race, combat exposure, drink-years, marital status, education, organic psychotic conditions, other psychoses, neurotic personality and other nonpsychotic disorders, substance abuse, and use of psychotropic medications.

The results of the alternative analyses, using dioxin quintiles, were consistent with the results using dioxin categories for both the 1982 and 2002 examinations. The mean difference between the fifth and first quintiles (fifth minus first) was significantly different from zero for the 1982 WMS immediate recall Logical Memory task (immediate recall: mean difference=−0.45, 95% confidence interval [CI]=−0.88 to −0.03, *p*-value=0.04). The 1982 WMS delayed recall Logical Memory task also was significantly different from zero (delayed recall: mean difference=−0.41, 95% CI=-0.81 to 0.00, *p*-value=0.05), as noted in the previous article on memory in AFHS veterans (Barrett et al., 2001). No statistically significant differences were found in the analysis of the 2002 examination data.

When analysis was restricted to enlisted groundcrew, the military occupation cohort with the highest average levels of exposure to dioxin, no significant differences were observed in either the analysis of 1982 or 2002 examination data.

As described in the Data Analysis section, a different strategy was used when the memory scales from the 1982 and 2002 examinations were contrasted with each other because of the inherent difference in the scoring methods. Analysis results for the contrast of the 1982 and 2002 examination memory scales were based on standardized scores for the 1982 and 2002 examinations. The mean and standard deviations for each memory scale were determined at each examination and the scores from the memory scales were standardized by subtracting the mean from each score and dividing by the standard deviation.

A repeated measures analysis using an autoregressive order 1 covariance structure was used to determine if the relation between the memory scale and dioxin changed across examinations (Littell et al., 1996). If there was no significant change across examinations, the association between dioxin exposure and the memory scale was examined with the data from both examinations pooled together. As expected, a difference existed between examinations on the immediate and delayed recall scales. Ranch Hand veterans in the high category scored significantly lower than comparison veterans on both the immediate and delayed recall trials of the WMS Logical Memory subtest at the 1982 examinations, but there was no difference between Ranch Hand veterans and comparisons on these two WMS-R scales at the 2002 examination. For the immediate and delayed recall Visual Reproduction scales and the Verbal Paired Associates scale, there was no association between dioxin and the score on these memory scales.

To further investigate any differences between results on the Verbal Paired Associates, Logical Memory, and Visual Reproduction memory scales, pairs were constructed for each individual who was tested at both the 1982 and 2002 examinations. The 2002 standardized score on each scale was subtracted from the 1982 standardized score on each scale. Constructing a difference score reduces the total variation by eliminating the inter-veteran variation.

The relation between the difference of standardized scores and dioxin was analyzed after adjustment for body mass index at time of the dioxin blood draw, military occupation (officer, enlisted flyer, enlisted groundcrew), date of birth, race (black, non-black), and combat exposure quartile. These covariates did not change between the two examinations. Table 7 shows the results of this analysis. If a veteran's memory had

decreased across time, the difference score would be positive. If a veteran's memory had increased across time, the difference score would be negative. For the delayed recall logical memory, the difference between Ranch Hands in the high dioxin exposure category and comparisons was significant, but the analysis showed that the average comparison memory score had decreased across time (positive difference score) and, for Ranch Hands in the high dioxin exposure category, the average memory score had increased across time (negative difference score). Therefore the significant change in memory scores across time was adverse to comparisons rather than Ranch Hands in the high dioxin exposure category.

When analysis was restricted to enlisted groundcrew, the difference between Ranch Hands in the high dioxin category and comparisons was significant for both the immediate recall logical memory ($p=0.03$) and the delayed recall logical memory ($p<0.01$). The analysis on enlisted groundcrew only, however, showed similar patterns to the analysis based on all participants. The average comparison memory score (both immediate and delayed recall) had decreased across time (positive difference score) and, for Ranch Hands in the high dioxin exposure category, the average memory score had increased across time (negative difference score). Therefore the significant change in memory scores across time was adverse to comparisons rather than Ranch Hands in the high dioxin exposure category.

Table 7. Adjusted[a] Wechsler memory scale results by dioxin category for the difference between paired 1982 and 2002 examination standardized[b] scores

Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
Verbal Paired Associates				
Sample Size	845	309	194	200
Adjusted Mean Difference Score[a,c]	-0.06	-0.06	-0.04	-0.08
Difference of Means[d]	0	0.01	0.02	-0.02
95% Confidence Interval		-0.13,0.14	-0.14,0.18	-0.18,0.15
P-value		0.93	0.80	0.85
Logical Memory				
Immediate Recall				
Sample Size	806	295	187	189
Adjusted Mean Difference Score[a,c]	0.07	0.06	0.02	-0.09
Difference of Means[d]	0	0	-0.04	-0.16
95% Confidence Interval		-0.14,0.14	-0.21,0.12	-0.32,0.01
P-value		0.95	0.61	0.07
Logical Memory				
Delayed Recall				
Sample Size	824	303	197	194
Adjusted Mean Difference Score[a,c]	0.14	0.18	0.03	-0.10
Difference of Means[d]	0	0.03	-0.12	-0.25
95% Confidence Interval		-0.11,0.18	-0.28,0.05	-0.42,-0.07
P-value		0.65	0.17	**0.01**
Visual Reproduction				
Immediate Recall				
Sample Size	842	308	198	201
Adjusted Mean Difference Score[a,c]	0.05	0.11	0.05	0.08
Difference of Means[d]	0	0.06	0	0.03
95% Confidence Interval		-0.08,0.20	-0.16,0.16	-0.13,0.20
P-value		0.41	0.98	0.71
Visual Reproduction				

Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
Delayed Recall				
Sample Size	846	311	199	201
Adjusted Mean Difference Score[a,c]	0.03	0.10	0.00	0.04
Difference of Means[d]	0	0.07	-0.03	0.01
95% Confidence Interval		-0.07,0.21	-0.19,0.13	-0.15,0.18
P-value		0.34	0.70	0.89

[a]Adjusted for body mass index at time of the dioxin blood draw, military occupation, date of birth, race, and combat exposure.

[b]The standardized score was determined separately for each examination by subtracting the mean score from each individual score at the examination and dividing by the standard deviation of the scores at the examination.

[c]The mean difference score is determined by subtracting the 2002 standardized score from the 1982 standardized score and taking the arithmetic average of these differences.

[d]Difference of means is the difference of the adjusted mean difference score from the adjusted mean difference score for comparisons. A positive difference of means indicates an adverse effect to Ranch Hands relative to comparisons. A negative difference of means indicates an adverse effect to comparisons relative to Ranch Hands.

DISCUSSION

The results of this study indicate that Agent Orange-exposed Ranch Hand veterans are functioning normally in regards to immediate and delayed memory. There does not appear to be any long-term adverse effect in regards to memory functioning. While the 1982 examination found small memory deficits in the highest exposed veterans, the 2002 examination indicates that the memory deficit is no longer apparent. The specific neurological mechanisms (e.g., structural, neurochemical, or other) related to the cause of the 1982 deficits in memory are unknown; however, these changes likely have been reversed. In addition, we cannot rule out the possibility that the 1982 findings were due to chance.

Human memory demonstrates an ability to recover following exposure to toxic substances. Alcohol abusers display improved memory following abstinence in a matter of weeks. Exposure to polychlorinated biphenyls in adulthood has been linked to memory deficits that were alleviated with treatment (Kilburn et al., 1989). Pelcolva et al. (2001) found that the most highly exposed dioxin subjects demonstrated deficits more than 30 years following exposure with a correlation between levels of exposure and extent of the deficit. The less exposure, the better the memory functioning. The elimination of dioxin from a person over time decreases his ongoing exposure that may be reflected in improved memory functioning. The fact that there are no memory deficits evident 35 years after exposure is consistent with the recovery ability of the human brain.

Studies that have examined the neuropsychological effects of exposure to Agent Orange have found varying degrees of negative effects involving some aspect of memory (Levy, 1988; Fiedler and Gochfeld, 1992; Barrett et al., 2001). While there may be some concern that the findings of decreased logical memory functioning in Ranch Hands with the highest exposure may have been due to the inexact scoring protocols used for the WMS, these potential scoring difficulties also could have caused false negatives and masked effects of dioxin on memory functioning in other areas. The improved scoring criteria that are part of the WMS-R do not make the findings for the 1982 examination less substantive, but they do reduce the chance of a false negative. Our study addresses the concern raised by the National Academy of Sciences that there may be an “accelerated aging” process due to the impact of herbicide exposure in conjunction with the normal age related memory decline (Institute of Medicine, 1994). Many of the exposed veterans have reached age 60 and, to date, have not displayed any significant memory deficits when compared to unexposed veterans.

REFERENCES

Barrett DH, Morris RD, Akhtar FZ, Michalek JE. Serum dioxin and cognitive functioning among veterans of Operation Ranch Hand. NeuroToxicology 2001;22:491-502.

Board of the American Society of Health-System Pharmacists. AHFS drug information. Bethesda, MD: American Hospital Formulary Service, 2000.

Fiedler N, Gochfeld M. Neurobehavioral correlates of herbicide exposure in Vietnam veterans: A report on the Pointman Projects to the New Jersey Agent Orange Commission, 1992.

Grubbs WD, Lustik MB, Brockman AS, Henderson SC, Burnett FR, Land RG, Osborne DJ, Rocconi VK, Schreiber ME, Williams DE. Air Force Health Study: An epidemiologic investigation of health effects in Air Force Personnel following exposure to herbicides. NTIS AD A-304-306 through AD A-304-316. Springfield: National Technical Information Service, 1996. pp. 2–14.

Hornung RW, Reed DR. Estimation of average concentration in the presence of nondetectable values. Appl Occup Environ Hyg 1990;5(1):46-51.

Institute of Medicine. Veterans and Agent Orange. Washington: National Academy Press, 1994.

Kilburn KH, Warsaw RH, Shields MG. Neurobehavioral dysfunction in firemen exposed to polychlorinated biphenyls (PCBs): Possible improvement after detoxification. Arch Env Health 1989;44:345-50.

Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research. Principles and quantitative methods. New York: Van Nostrand, 1982. p. 455.

Levy CJ. Agent Orange exposure and post-traumatic stress disorder. J Nerv Ment Dis 1988;176:242–5.

Littell RC, Milliken GA, StroupWW, Wolfinger RD. SAS® System for Mixed Models. Cary, NC: SAS Institute Inc., 1996.

Michalek JE, Tripathi RC. Pharmacokinetics of TCDD in veterans of Operation Ranch Hand: 15-year follow-up. J Toxicol Environ Health 1999;57(6):369-78.

Pelclova D, Fenclova Z, Dlaskova Z, Urban P, Lukas E, Prochazka B, Rappe C. Biochemical, neuropsychological, and neurological abnormalities following 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exposure. Arch Env Health 2001;56:493–500.

Peper M, Klett M, Frentzel-Beyme R, Heller W. Neuropsychological effects of chronic exposure to environmental dioxins and furans. Environ Res 1993;60:124-35.

Prigatano GP. The Wechsler Memory Scale is a poor screening test for brain dysfunction. J Clin Psychol 1977;33(3):772-7.

Prigatano GP. Wechsler Memory Scale: A selective review of the literature. J Clin Psychol 1978;34(4):816-32.

Puckett CD, editor. The educational annotation of ICD-9-CM. Reno: Channel Publishing Ltd., 1995.

Russell EW. A multiple scoring method for the assessment of complex memory functions. J Consult Clin Psychol 1975;43(6):800-9.

SAS/STAT® User's Guide, Version 8. Cary, NC: SAS Institute Inc., 1999.

Wechsler D. A standardized memory scale for clinical use. J Psychol 1945;19:87-95.

Wechsler, D. Wechsler Memory Scale-Revised. San Antonio, TX: The Psychological Corporation, 1987.

Wechsler D. Wechsler Memory Scale-Third Edition. San Antonio, TX: The Psychological Corporation, 1997.

Wolfe WH, Michalek JE, Miner JC, Rahe A, Silva J, Thomas WF, Grubbs WD, Lustik MB, Karrison TG, Roegner RH, Williams DE. Health status of Air Force veterans occupationally exposed to herbicides in Vietnam: I. Physical health. JAMA 1990;264:1824–31.